REMARKS

This Amendment and Remarks are filed in response to the First Office Action dated March 29, 2006, wherein all claims stand rejected.

Rejections Under 35 USC § 112

Claims 1-21 are rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Examiner argues that in claim 1 and where recited in other claims, "*in situ* formation of a superficial cartilage layer", "superficial cartilage", "neo-cartilage" and "neo-cartilage construct" are uncertain as to meaning and scope. It is uncertain how "*in situ* formation" defines the method in addition to the process steps recited. What is the difference in superficial cartilage and neo-cartilage from other cartilage, and how does one know when the cartilage exists as compared to other cartilage?

Applicants disagree that the above terms are indefinite. The questioned terms and difference between mature cartilage (i.e. normal healthy cartilage), immature neo-cartilage, neo-cartilage construct and superficial cartilage layer are explained in the specification, for example on page 20, lines 2-16, and defined in the Definition section, specification, pages 11-16.

However, for Examiner's benefit and understanding, Applicants summarize conditions leading to this invention and add the following explanations of terms.

Cartilage is a connective tissue covering joints and bones. The utmost covering tissue layer of the joint cartilage is called synovial membrane. When the joint is injured such that for example there is an injury causing a cartilage rupture, cavity or lesion, not only the cartilage itself but also a continuity of the synovial membrane is disrupted.

The invention concerns a repair of the cartilage lesions including development of the superficial cartilage layer that

repairs disrupted synovial membrane. The method according to the invention and current claims are directed toward repairing such ruptured lesion by providing a neo-cartilage construct and also repairing the damaged synovial membrane by providing conditions for formation of the superficial cartilage layer. The superficial cartilage layer is thus a covering layer bridging two sides of the ruptured synovial membrane. The superficial cartilage layer develops from the second sealant deposited over the neo-cartilage construct that is formed between two sides of a disrupted synovial membrane.

Cartilage is a mature tissue comprising metabolically active but non-dividing chondrocytes. The mature cartilage thus maintain its *status quo*, that is it functions as a cartilage as long as it is not damaged or degenerated. However, the mature cartilage is avascular, that is it is totally or almost totally devoid of any blood supply and, therefore, because the chondrocytes in the mature cartilage are non-dividing, the mature cartilage cannot repair itself. The mature chondrocytes cannot activate themselves without extraneous intervention.

Neo-cartilage is an immature cartilage comprising metabolically activated chondrocytes which are able to divide and multiply. During development of this invention, it was discovered that under certain conditions described in the specification on pages 22-34, the chondrocytes could be activated from static non-dividing stage to an active stage where they divide, multiply, promote growth of the extracellular matrix and develop into new cartilage (neo-cartilage). The neo-cartilage thus contains chondrocytes which were rejuvenated and are surrounded by a newly synthesized extracellular-matrix macromolecules. A process for activation of chondrocytes comprises isolation of chondrocytes (Spec., page 23 (a)), expansion of chondrocytes (Spec., page 24 (b)), suspension of expanded chondrocytes in a support matrix (Spec., page 24 (c)) and subjecting the chondrocytes-support matrix construct to processing in a tissue processor (Spec., page 33

(D)).

Differences between the mature and neo-cartilage is in their maturity and ability to divide, expand and multiply.

Neo-cartilage is an immature cartilage which eventually, upon deposition into the lesion according to this invention, is integrated into and acquires properties of a mature hyaline cartilage.

This invention utilizes properties of neo-cartilage in achieving repair and restoration of damaged cartilage into the full functionality of the healthy cartilage by enabling the neo-cartilage to be integrated into the native hyaline (mature) cartilage surrounding the lesion wherein such newly integrated neo-cartilage is covered with the superficial cartilage layer that develops within 2-3 months substituting, in a way, for the synovial membrane.

Synovial membrane is defined in Medical Dictionary as a layer of connective tissue that covers joints, tendon sheaths, and bursae. Synovial membrane is a delicate and thin layer that constitutes part of the articular capsule of a synovial joint.

Superficial cartilage layer formed under conditions of this invention is an outermost layer of cartilage that forms the layer of squamous-like flattened superficial zone chondrocytes covering and overgrowing the lesion. The superficial cartilage layer is outgrowing from the layer of the second sealant deposited over the neo-cartilage placed into the lesion. The superficial cartilage layer is thus a tissue found, in time, usually within 2 months following the surgery and deposition of the second sealant, on the surface of treated lesion that resembles in its function the synovial membrane and is eventually integrated there.

To practice the invention, the bottom of the lesion is typically first covered by a first sealant, the neo-cartilage construct is deposited into the lesion and the second sealant is deposited over the construct. The deposition of the first sealant is optional.

The superficial cartilage layer is a product of a second top sealant placed over and covering the treated lesion. Sealant used in this invention is a biologically acceptable typically rapid-gelling synthetic compound having adhesive properties, and is a derivatized polyethylene glycol (PEG) cross-linked with a collagen compound, such as cross-linked PEG with methylated collagen.

It is believed that Applicants provided sufficient explanation of terms deemed to be indefinite. However, Applicants also extensively amended claims to make the terms appearing in these claims to be more definite.

Examiner also rejects dependent claims 5-21 as being unclear as to how they further limit the steps of claim 1. It is unclear as to what steps these claims require being added to claim 1, and how these added steps are combined with the steps of claim 1.

Applicants disagree. However, following the amendment of the instant claims, it is believed that this rejection is now moot.

Rejections Under 35 USC § 103

Claims 1-21 are rejected under 35 USC 103(a) as being unpatentable over Smith et al (6,528,052 B1).

Examiner submits that the claims are drawn to a method of *in situ* formation of cartilage layer over an articular cartilage lesion by preparing a cartilage construct from isolated and expanded chondrocytes, implanting the construct, and depositing a sealant over the construct.

Smith et al disclose formation of cartilage *in vitro* from chondrocytes and implanting the cartilage (Col. 16, lines 40-55).

It would have been obvious to seal with a sealant after implanting to prevent contamination of the site of implantation. The cartilage produced before implanting is inherently a construct. A hydrostatic pressure as in claim 12 is disclosed by Smith et al. Embedding chondrocytes in a matrix as in claim 3 would have been obvious since using a matrix as claimed is known in the prior art.

Applicants disagree. Formation and development of the superficial cartilage layer similar to that of the synovial

membrane as an outgrowth of the second sealant deposited over the neo-cartilage construct is totally unexpected. It is not achieved with every biological sealant and the whole process of the development and formation of said superficial cartilage layer and its integration into surrounding synovial membrane depends on the combination of the emplacement of the neo-cartilage construct comprising activated chondrocytes into the lesion and covering the lesion with the second sealant that is a PEG cross-linked with collagen, particularly with methylated collagen. While the depositing the covering sealant may seem to be obvious thing to do, it is not obvious that this sealant will form the superficial layer covering the newly formed cartilage and having properties of the synovial membrane.

Smith reference and claims are directed to a method for *in vivo, ex vivo* or *in vitro* repair and regeneration of diseased or injured cartilage or for *de novo* production of cartilage, collagen, ligament or tendon by submitting the degenerated or diseased cartilage to intermittently applied hydrostatic pressure at certain specific values. Smith does not disclose anywhere in the specification or claims use or need for a any tissue sealant and such use of one or two sealants is not contemplated or suggested by Smith reference. The superficial cartilage layer, its existence or formation is also not disclosed by Smith reference. Need for covering the Smith's implant by a sealant or insulating the lesion cavity before implanting his implant in the lesion has not been disclosed.

Smith reference merely deals with a regimen comprising periods of intermittently applied hydrostatic pressure followed or interspaced with resting periods. This regimen has been proven to lead to regeneration of the diseased cartilage and to activation of inactive chondrocytes. Thus at most, the Smith reference may lead to preparation of the neo-cartilage construct but does not disclose any sealant, need for such sealant, need for the implant insulation or formation of any covering membrane.

The current invention is based on discovery that the cartilage lesions can be repaired by providing a neo-cartilage construct deposited into the cartilage lesion that has been already treated with a first (bottom) layer of the tissue sealant deposited on the bottom of the lesion. The neo-cartilage that may or may not be pre-treated with the regimen of the intermittently applied hydrostatic pressure as described by Smith, is placed in the lesion cavity covered optionally with the first sealant and covered with a second tissue sealant. These steps can only be performed *in situ* during surgery.

Under conditions of the instantly claimed method, when the second layer is deposited over the lesion now filled with neo-cartilage and will, in time, form a continuous uninterrupted superficial layer overgrowing the lesion and protect the implanted neo-cartilage construct during its integration into the surrounding native hyaline cartilage. Additionally, it has been discovered that the second sealant layer begins to integrate itself into the synovial membrane covering the joint. Such integration results in development of the superficial cartilage layer and typically happens in 2-3 months.

Applicants provide authentic microphotographs of the superficial cartilage layer developing after the knee surgery in experimentally treated porcine knee joint with the neo-cartilage construct according to the invention. Figures 10B, 12A and 12B illustrate this process and clearly show the formation of the superficial cartilage layer in treated lesion compared to untreated lesion where such superficial cartilage is not observed.

Claims 1-21 are amended. It is respectfully submitted that the claims are not obvious from the Smith reference. The rejection should be withdrawn and claims allowed. It is so respectfully requested.

Obviousness Double Patenting Rejections

Claims 1-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

claims 1-16 of U.S Patent No. 6,949,252 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed method of forming cartilage would have been obvious from the method claimed by the patent of preparing an implantable tissue construct for treatment of a cartilage lesion.

Applicants disagree. As already argued above, Smith claims are directed to a method for *in vivo, ex vivo or in vitro* repair and regeneration of diseased or injured cartilage or for *de novo* production of cartilage, collagen, ligament or tendon by submitting the degenerated or diseased cartilage to intermittently applied hydrostatic pressure at certain specific values. The superficial cartilage layer, its existence or formation, tissue sealants and their use are not claimed by Smith. Smith's claims are directed to a method for *in vivo, ex vivo*, or *in vitro* repair and regeneration of diseased cartilage using a regimen comprising periods of intermittently applied hydrostatic pressure followed by recovery resting periods. This regimen has been proven to lead to regeneration of the diseased cartilage.

The current claims claim formation of the superficial cartilage layer as described above.

It is respectfully submitted that the claims are patentably distinct and not obvious from the Smith claims and that there is no non-statutory obviousness between both sets of claims. Rejection should be withdraw. It is so respectfully requested.

Inventorship

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the

examiner to consider the applicability of 35 USC 103(c) and potential 35 USC 102(e), (f) or (g) prior art under 35 USC 103(a).

All inventors remain the same.

SUMMARY

In summary, claims 1-21 are amended, arguments are provided to overcome rejections under 35 USC 103 and rejection based on non-statutory double patenting rejection.

Respectfully submitted,

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